COMMENTARY

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Insights into the potential role of alpha1-antitrypsin in COVID-19 patients: Mechanisms, current update, and future perspectives

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Abstract

In this work, we provide an up-to-date summary of the available molecular- and cell-related mechanisms by which alpha1-antitrypsin (AAT) protein could be of benefit in treating COVID-19 patients. As well, we demonstrate the current status in terms of the ongoing clinical trials using AAT in COVID-19 patients. Finally, we touch on the potential role gene therapy and stem cell-based gene therapy could have in such emerging and serious condition caused by the SARS-CoV-2 virus.

1 | INTRODUCTION

Since its first discovery in the city of Wuhan (China), the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been notorious of its high infectivity, and high mortality due to respiratory failure causing an escalating worldwide health emergency.[1]

Recently, Vianello and Braccioni have made their early notion about the potential correlation between disease severity and high fatality of SARS-CoV-2 to the pre-existence of alpha-1 antitrypsin deficiency (AATD),[2] supported by remarkable matching between the geographic distribution of confirmed AATD cases and that reported for SARS-CoV-2 infection. The proposed association between AATD and COVID-19 might reveal subtypes of COVID-19 patients who might benefit from alpha1-antitrypsin (AAT) supplementary therapy, thus merits further emphasis.

The AAT protein is a serine protease inhibitor that is secreted by hepatocytes to perform its major role in the lower respiratory tract where it provides most of the tissue defenses against injurious proteolytic action of proteases (e.g., neutrophil elastase, cathepsin G, and proteinase-3, etc.).[3] Moreover, the AAT protein is acknowledged for being one of the key players in the acute phase anti-inflammatory response.[4] Therefore, individuals with AATD were found to lack control over various inflammatory mediators, as interleukin (IL)-6, IL-1β, IL-8, and tumor necrosis factor (TNF)-α. On the other side, the high mortality in COVID-19 patients is associated with respiratory failure (due to acute respiratory distress syndrome [ARDS]) and/or multi-organ failure due to the striking "cytokine storm,"[5] where levels of cytokines as IL-1b, IL-2, IL-7, IL-8, IL-9, IL-10, IL-17, G-CSF, GMCSF, IFNγ, TNFα, IP10, MCP1, MIP1A, and MIP1B have gone through the roof. In addition, excessive infiltration of the inflammatory cells (e.g., monocytes and neutrophils) into the pulmonary interstitial tissue. provoked cytokine-induced apoptosis of alveolar lining cells (i.e., pneumocytes).[6] In addition, single nucleotide polymorphisms (SNPs) of SERPINA1 gene which encodes α1-antitrypsin related to increased risk of ARDS and mortality.[7]

All authors contributed equally to the manuscript.

2 | MECHANISMS

Even though AATD state as such is not a disease, it is considered a distinct genetic predisposition to the development of several other diseases. Therefore, a common thread seems to connect individuals with AATD and the aggressive course of SARS-CoV-2 infection. In addition to its prime inhibitory function against serine proteinases evading tissue damage, AAT is known to abrogate inflammation via both enzyme inhibitory and non-inhibitory roles.[8] Table 1 summarizes the up-to-date proposed mechanisms by which AAT could be beneficial in COVID-19 patients.

3 | CURRENT STATUS

With the mounting evidence of possible association between AATD and COVID-19,[9] the logic consequence has been to

TABLE 1 Potential mechanisms for the proposed therapeutic applications of AAT in COVID-19 patients

Role of AAT protein	Relevant role in COVID-19	Potential applications/mechanisms of AAT in COVID-19 patients
AAT inhibits neutrophil elastase as a serine proteinase.[24]	Neutrophil elastase induces the release of IL-8 from neutrophil vesicles and facilitates conversion of pro-IL-1β to IL-1β.[25]	AAT to mitigate IL-1β-induced acute lung injury.[8,25]
AAT antagonizes thrombin and plasmin.[26]	Thrombin and plasmin play central role in thrombosis, infection and host responses. Patients with COVID-19 have increased plasma thrombin and plasmin potential compared with healthy donors.[27]	AAT to guard against thrombotic complications observed in patients with COVID-19, including macrothrombi and small vessel thrombosis associated with disease progression, organ failure, and poor outcomes.
AAT decreases the levels and activity of IL-6.[28]	• IL-6 drives immune dysregulation and respiratory failure in COVID-cytokine storm syndrome.[29] • IL-6 elevation might have a role in endothelial activation and precipitation of a pulmonary immune-mediated thrombosis.[28] • The higher ratio of IL-6: AAT is seen in patients with the severe/critical COVID-19 disease.	• AAT to limit the "cytokine storm". • AAT augmentation as an immune modulator to reduce the pro-inflammatory cytokines, as IL-6.[28]
AAT binds to IL-8, preventing from binding to its receptor CXCR1 and activating Akt signaling pathway.[30]	Increased score of IL-8 is linked to a lethal cytokine storm and pathological phenotypes in COVID-19 patients.[31]	AAT to sequester IL-8, to limit both neutrophil influx and acute lung injury.
AAT inhibits host cell transmembrane protease serine 2 (TMPRSS2) receptors.[32]	TMPRSS2 receptors processes the SARS-CoV-2 spoke (S) protein, allowing protein–ACE2 interaction inducing SARS-CoV-2 virus uptake.[33]	AAT to limit the uptake of SARS-CoV-2 by inhibiting extracellular proteases on the host cells.
AAT inhibits disintegrin/metalloproteinase 17 (ADAM17).[32]	ADAM17 is a protease causing shedding of ACE2 (to hamper viral entry).[34] ADAM17, as a cell surface metalloprotease, cleaves membrane-bound TNF-α to soluble TNF-α. Increased serum levels of soluble TNF-α receptor is associated with mortality of ICU COVID-19 patients.[35]	AAT to limit the uptake of SARS-CoV-2 virus particles. AAT to harness the level of TNF-α and guard against diffuse inflammatory tissue damage.[36]

(Continues)

TABLE 1 (Continued)

Role of AAT protein	Relevant role in COVID-19	Potential applications/mechanisms of AAT in COVID-19 patients
AAT increases macrophage cells polarization toward the M2 phenotype.[37]	While M1-like macrophages secrete of pro-inflammatory cytokines (e.g., IL-6, TNF-α, and IL-1β) that cause the "cytokine storm," M2-like macrophages are critical to heal tissue damage at the aftermath of SARS-CoV-2 infection.[38]	AAT, as an immune modulator, to induce balanced antiviral immune response that leads to successful pathogen clearance without tissue damage.
AAT favors the differentiation of T lymphocytes toward the Treg phenotype.[8,39]	Tregs might play a direct pro-inflammatory role during the severe phase of COVID-19.[40]	AAT as an immunomodulator to limit the "cytokine storm" and inflammation-mediated severe lung damage.[41]
AAT depicts an intracellular antiproteolytic activity by binding and inactivating active caspase-3, circumventing alveolar cell (i.e., pneumocytes, endothelial, or myofibroblast) injury/death.[42]	Activated caspase-3 is a marker of caspase-dependent apoptosis seen in tissues of severe COVID-19 patients due to various SARS-CoV-2-encoded accessory protein (e.g., ORF3a, ORF-3b, ORF-6 and ORF-7a).[43,44]	AAT to protect against caspase-3-induced alveolar wall destruction and oxidative stress.[42,45]
AAT suppresses TGF-β/Smad3 signaling.[46]	SARS-CoV-2 spike binds to its receptor and activates the TGF-β pathways, triggering inflammation, apoptosis, and fibrosis, which led to severely damaging effects in lungs and other tissues of COVID-19 patients.[21]	AAT to mitigate TGF-β-induced immediate and long-term damaging effects of COVID-19.[21]
AAT controls ATP-induced IL-1β release from human mononuclear white blood cells by a triple-membrane-passing signaling pathway involving CD36, iPLA2β, and nAChR.[47]	IL-1β induces generation of other cytokines, including IL-6 and TNF-α, thereby contributing to the "cytokine storm."[48]	AAT to mitigate the hyperinflammatory nature "cytokine storm" of COVID-19.[25]
AAT suppresses superoxide production by activated neutrophils.[49]	SARS-CoV-2 infection pathogenesis is related to oxidative stress that perpetuates the cytokine storm cycle, blood clotting mechanism, and exacerbates hypoxia and organ failure.[50]	AAT to reduce oxidant-driven amplification of inflammation.
AAT reduces neutrophil chemotaxis which may well reflect its ability to inhibit cellular cathepsin G activity.[30]	Neutrophil recruitment and related activity might exacerbate COVID-19 immunopathology.[51]	AAT to modulate the recruitment of neutrophils and hence the downstream inflammatory response driven them and their products.

validate if COVID-19 patients could benefit from AAT supplementary therapy. Being an FDA-approved drug with a remarkable clinical safety record,[10] AAT is currently tested in three registered interventional clinical trials as summarized in Table 2. In addition to the AAT, several other serine protease inhibitors might be of benefit in COVID-19 patients since host proteases could facilitate viral entry, replication and eventually mediate the pathogenesis of viral infections, such as SARS-CoV-2. Therefore, protease inactivators are being recently considered as potential antiviral drugs for

treatment of COVID-19.[11] Ulinastatin, another intrinsic trypsin inhibitor, has significant anti-inflammatory action through decreasing the plasma levels of TNF-α, IL-6, and C-reactive protein. Moreover, it has significant anti-oxidative effects through lowering the level of superoxide dismutase, malondialdehyde, justifying its clinical use in several disorders as the ARDS as it improves lung function, oxygenation, and eventually shortens the period of mechanical ventilations and total hospital stay. Interestingly, high doses of ulinastatin were recently administered via intravenous infusion and are

TABLE 2 Clinical trials on the impact of AAT treatment in COVID-19 cases

Status	Study title	Interventions	Phase	Start date	Location(s)
Recruiting	Study to Evaluate the Safety and Efficacy of Prolastin in Hospitalized Subjects With COVID-19	• Biological: Prolastin (Alpha1-proteinase inhibitor) Intravenous infusion 120 mg/kg • Drug: SMT per local guidelines	Phase 2	July 29, 2020	• Hospital Germans Trias Badalona, Spain • Hospital Clínic Barcelona, Spain • Hospital Valle de Hebrón Barcelona, Spain • +4 more
Recruiting	Study to Evaluate the Safety and Efficacy of Liquid Alpha1-Proteinase Inhibitor (Human) in Hospitalized Participants With COVID-19.	• Biological: Liquid Alpha1-Proteinase Inhibitor (Human) • Drug: Placebo • Drug: SMT	Phase 2	Jan 2021	• Birmingham VA Birmingham, Alabama, USA • CHI Health Center Omaha, Nebraska, USA • Columbia University Medical Center New York, USA • +5 more
Recruiting	Trial of Alpha One Antitrypsin Inhalation in Treating Patient with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)	• Drug: 8 ml of intravenous alpha one antitrypsin (alpha1-proteinase inhibitor (AATD) Glassia 50 ml) as nebulizer/12 h for 5 days. • Placebo: 8 ml of normal saline as nebulize/12 h for 5 days	Early Phase 1	June 1, 2020	• Ministry of Health Mecca, Saudi Arabia

Note: Available at: https://clinicaltrials.gov/ (last access on 30, Jan 2021).[52]

Abbreviation: SMT, standard medical treatment.

being suggested to have a beneficial impact on patients with COVID-19.[12-14]

4 | FUTURE PERSPECTIVES

The better understanding of specific infection pathways of SARS-CoV-2 virus into the host cells, as well as mechanisms in the development of a fatal "cytokine storm" has encouraged several research groups to investigate the potential use of mesenchymal stem cells (MSCs) to control such excessive immune reaction thanks to their side-effect free immunomodulatory effect.[15-17]

Moreover, MSC engineering appears to be a promising strategy to overexpress AAT that could be used to treat AATD, or to augment AAT in patients with normal AAT plasma levels.[18] This approach is quite flexible as patients might benefit from the versatile secretome of MSCs, in addition to the AAT expression.[19]

Other than AAT gene transfection, MSCs could be also co-transfected with other genes that could be of benefit to COVID-19 patients, such as the bone morphogenetic protein (BMP) 7 gene.[20] BMP7 is a secreted protein that belongs to the TGF-β superfamily and regulates cell proliferation, differentiation, apoptosis, and antagonizes TGF-β signaling and its actions which may be of benefit in the treatment of COVID-19-related multiorgan injuries.[21]

If fact, myriad virus-based gene delivery trials were conducted using various virus carriers. Nevertheless, results obtained did not achieve protective levels of AAT expressed in the lung interstitium.[22] Moreover, the nonspecific targeting of viral/non-viral gene carriers and their systemic administration were found to bring about unsought off-target adverse effects. Therefore, MSC-based gene therapy could be a promising therapeutic strategy to circumvent the problem of targeted delivery and sufficient level of gene expression,[15] especially when we know that most of the intravenously administered MSCs seem to be trapped in the lungs during the first pass.[23]

CONFLICT OF INTEREST
The authors report no conflicts of interest in this work.

AUTHOR CONTRIBUTIONS
All authors have contributed equally to the conceptualization, writing and review of the manuscript.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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